PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference MP101105-WO	**FOR FURTHER ACTION**	See Form PCT/IPEA/416
International application No. PCT/GB2004/003104	International filing date *(day/month/year)* 19.07.2004	Priority date *(day/month/year)* 19.07.2003
International Patent Classification (IPC) or national classification and IPC A61K9/50, A61K9/70, A61K33/14, A61K31/60, A61K31/155		
Applicant WARD, Warren		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 7 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☒ *sent to the applicant and to the International Bureau)* a total of 1-5 sheets, as follows:
      ☒ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

☒	Box No. I	Basis of the opinion
☐	Box No. II	Priority
☐	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☐	Box No. VIII	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
25.01.2005	10.11.2005
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Schifferer, H Telephone No. +49 89 2399-7472

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/GB2004/003104

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3 and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4)
   - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

Description, Pages	
1-33	as originally filed
Claims, Numbers	
1-34	received on 18.02.2005 with letter of 16.02.2005
Drawings, Sheets	
1/3-3/3	as originally filed

   ☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/GB2004/003104

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-34
	No:	Claims	-
Inventive step (IS)	Yes:	Claims	1-34
	No:	Claims	-
Industrial applicability (IA)	Yes:	Claims	1-34
	No:	Claims	-

2. Citations and explanations (Rule 70.7):

see separate sheet

V Reasoned statement under Rule 66.2 (a) (ii) with regard to novelty, inventive step or industrial applicability

1) Amendments - Article 19 (2) PCT
The application has been amended by submitting claims 1-34 with the letter of February 16th, 2005. The amendments are considered acceptable according to Article 19 (2) PCT on the basis of former claims 1,3 and page 6, lines 23-26 of present description. Therefore, the set of claims of February 16th, 2005 is referred to as basis for further examination.

2) Search
In view of the description and the explanations provided with the letter of February 16th, 2005, the search for this patent application is regarded as complete and appropriate.

3) Clarity

3.1) By referring to sodium chloride and not to the word "use" in former dependent claims 9-12 , the concerns of 2.1 a) in the written opinion of December 6th, 2004 have been resolved.

3.2) Claims 1-7, 13-18 do not meet the requirements of Article 6 PCT in that the matter for which protection is sought is not clearly defined. The claims attempt to define the subject-matter in terms of the result to be achieved, - namely by expressing that said composition/compound is suitable for the treatment of medical conditions at least partially characterised by blockage or other malfunction of exocrine glands (see claims 1, 13) - which merely amounts to a statement of the underlying problem, without providing the technical features necessary for achieving this result. In view of 2.4, it does not seem that the diseases which are summarized under this term on page 9, lines 12-26 in present description are really covered by the above term under consideration of offcial pathological classification.

3.3) The feature that sodium chloride cannot cross epithelial barriers (see claim 1, 27) has been deleted from the corresponding claims, the clarity concern thus seems to be resolved (Article 6 PCT).

3.4) Based on explanations provided in the letter of February 16th, 2005 (page 5) the expression of "a liquid impermeable, but gas permeable layer" is considered acceptable.

3.5) In addition, the diseases listed on page 9, lines 12-26 cannot be recognized as medical conditions at least partially characterised by blockage or other malfunction of exocrine glands. This discrepancy causes a lack of clarity according to Article 6 PCT and throws doubt on the exact scope of protection. Glaucoma is the disease of an increased eye pressure caused by a decreased outflow of aqueous humour through the pupil, trabecular meshwork and Schlemm's canal. which is not affected by exocrine glands itself. The description of the group of diseases intended does not correspond to the official pathological classification of the diseases themselves.

4) Documents

The following documents (D1-D5) are referred to in this communication; the numbering will be adhered to in the rest of the procedure:

D1: GB 2 119 244 A (ALZA CORP) 16 November 1983 (1983-11-16)
D2: SAITO K ET AL: "EFFECT OF IONIC INTERACTION ON THE ENTRAPPING OF DRUG INTO POROUS MICROSPHERES AND DRUG RELEASE CHARACTERISTICS" CHEMICAL AND PHARMACEUTICAL BULLETIN, PHARMACEUTICAL SOCIETY OF JAPAN. TOKYO, JP, vol. 35, no. 5, May 1987 (1987-05), pages 2045-2051, XP001182583 ISSN: 0009-2363
D3: WO 03/005995 A (AEROPHARM TECHNOLOGY INC) 23 January 2003 (2003-01-23)
D4: US 4 970 081 A (FRISBEE STEVEN E) 13 November 1990 (1990-11-13)
D5: US 2001/042932 A1 (CHICKERING DONALD ET AL) 22 November 2001 (2001-11-22)

Unless otherwise specified, reference is made to the respective cited passages in D1-D5 (see the International Search Report, Form PCT/ISA/210).

5) Novelty - Article 33 (1) and (2) PCT

5.1) D1-D4 disclose spheroid pharmaceutical forms comprising an active agent which is coated by a polymer revealing the following details:

D1
pharmaceutical form: tablet, capsule; active agent: potassium chloride, salicylic acid, salicylate salt; coating: vinylchloride-vinylacetate copolymer, magnesium lauryl sulphate or cellulose acetate

D2
pharmaceutical form: microsphere; active agent: salicylic acid; coating: graft polymers

D3
pharmaceutical form: tablet, core, sphere; active agent: metformin; coating: a layer of pioglitazone hydrochloride on at least a portion of a surface of said core, a further layer comprising a modulating polymer and at least one of said metformin or pioglitazone hydrochloride

D4
pharmaceutical form: granule; active agent: aspirin; coating: copolymer of ethyl acrylate and methyl methacrylate, hydroxypropylmethyl cellulose

D5
pharmaceutical form: microcapsule; active agent: salicylic acid; coating: pvp
or
pharmaceutical form: microsphere; active agent: protein; coating: bioadhesive polymers by phase inversion (poly(fumaric-co-sebacic acid))
A list of active compounds can be integrated in the proposed formulations including anti-acne, anti-allergic, anti-asthmatic, antihypertensive and antimigraine agents besides others.

In a further embodiment microspheres and nanospheres with microencapsulated sodium chloride crystals are prepared. The salt crystals are entirely entrapped by the microspheres.

After amending the claims with the letter of February 16th, 2005, D1-D5 do not disclose a) sodium chloride formulated coated with an agent that forms a liquid impermeable but gas permeable layer such that during therapeutic application in or on the body no metabolic, no chemical change and no reduction in its quantity can be recognised, b) its use for the manufacture of a medicament for the treatment of diseases caused by malfunction of exocrine glands, patches or another preparation based on the aforementioned compositional system.

5.2) In the light of D1-D5 (see sections V-4, 5.1) and under consideration of section V-1), 2), 3.1-3.5, the subject-matter of claims 1-34 appears to be novel (Article 33 (1), (2) PCT), since its corresponding content is not disclosed by D1-D5.

6) Inventive Step - Article 33 (1) and (3) PCT

6.1) The problem posed in the present application was the treatment of medical conditions at least partially charcterised by blockage or other malfunction of exocrine glands.

The solution according to the Applicant was a composition comprising an active agent (sodium chloride, any medically efficacious agent, in particular metformin, salicylic acid, derivatives thereof, capsaicin) coated with a substance that forms a liquid impermeable but gas permeable layer.

D5 which is regarded closest prior art discloses several compositions which are of relevance in connection with said invention:

a) Microspheres and nanospheres with microencapsulated sodium chloride crystals. The salt crystals are entirely entrapped by the microspheres.

b) Hydrophobic protein microspheres coated with bioadhesive polymers by phase inversion (poly(fumaric-co-sebacic acid))

c) Microcapsules where salicylic acid is encapsulated in polyvinylpyrrolidone

A list of active compounds can be integrated in the proposed formulations including anti-acne, anti-allergic, anti-asthmatic, antihypertensive and antimigraine agents besides others. Their use can be derived from the name of the classes. Hence, the use is covered by the list of diseases given on page 9, lines 12-26 in present description.

D5 does not disclose

a) a liquid impermeable and concurrently gas permeable layer

b) the exclusion of metabolic changes, chemical changes,diminution of the quantity of sodium chloride

c) a patch based on said spheres
d) a device consisting of a holder adapted for holding a medically efficacious compound, an energy source and an actuator
e) an implant based on said spheres
f) the treatment of exocrine gland diseases with sodium chloride.

Based on these differences and the letter of February 16th, 2005, it does not appear to be obvious to a person skilled in the art - when studying the prior art - to

- establish a clearly liquid impermeable, but gas permeable layer
- ensure the exclusion of metabolic, chemical and quantitative changes of sodium chloride during use
- combine the microspheres of D5 with the pharmaceutical form of a patch or an implant
- to combine such a patch with a specific device
- to use a device with such technical features as given in the application
- to select the diseases to be treated according to the agents used.

6.2) Therefore, under provision of V-1), 2), 3.1-3.5, the subject-matter of claims 1-34 is not obvious to a person skilled in the art due to D5 as well as due to general textbook knowledge and general experience. Thus the aforementioned subject-matter does not meet the requirements of Article 33 (1) and (3) PCT in that extent that it cannot be considered inventive.

7) Unity of invention - Rules 13.1, 13.2 PCT
Based on the explanations and the amendments of claims in the scope of the letter of February 16th, 2005, the common inventive concept rendered novel (compare with sections above 5.1, 5.2).
Therefore, the amended patent application of present status seems to fulfill the requirements of unity (Rules 13.1, 13.2 PCT).

CLAIMS

1. The use of sodium chloride formulated coated with an agent that forms a liquid impermeable but gas permeable layer such that during therapeutic application in or on the body the sodium chloride shows:

(i) no metabolic change;

(ii) no chemical change; and

(iii) no diminution in its quantity in the formulation;

in the manufacture of a medicament for the treatment of medical conditions at least partially characterised by blockage or other malfunction of exocrine glands.

2. The use according to claim 1 wherein the sodium chloride is in crystal form.

3. The use according claim 1 or 2 wherein the agent is a ceramic, a polymer or a natural wax.

4. The use according to claim 1 or 2 wherein the agent encapsulates sodium chloride to form a sphere.

5. The use according to claim 4 wherein the sphere is of a diameter between 1 mm and 10 mm.

6. The use according to claims 4 or 5 wherein the sphere comprises sodium chloride crystals coated with beeswax hardened with cornstarch and talc.

7. Sodium chloride formulated coated with an agent that forms a liquid impermeable but gas permeable layer such that during therapeutic application in or on the body the sodium chloride shows:

(i) no metabolic change;

(ii) no chemical change; and

(iii) no diminution in its quantity in the formulation;

in the manufacture of a medicament for the treatment of medical conditions at least partially characterised by blockage or other malfunction of exocrine glands.

8. Sodium chloride according to claim 7 wherein the agent is a ceramic, a polymer or a natural wax.

9. Sodium chloride according to claim 7 wherein the agent encapsulates sodium chloride to form a sphere.

10. Sodium chloride according to claim 9 wherein the sphere is of a diameter between 1 mm and 10 mm.

11. Sodium chloride according to either of claims 9 or 10 wherein the sphere comprises sodium chloride crystals coated with beeswax hardened with cornstarch and talc.

12. A patch suitable for adherence to skin containing coated sodium chloride according to any of claims 7-11 adapted for use in the treatment of medical conditions at least partially characterised by the blockage or other malfunction of exocrine glands.

13. The patch according to claim 12 comprising a sticking plaster suitable for adherence to skin.

14. The patch according to claim 13 comprising a hypoallergenic water resistant plaster.

15. The patch according to either of claims 13 or 14 in the form of a figure eight.

16. The patch according to claim 15 further comprising two spherical granules of sodium chloride.

17. A device consisting of a holder adapted for holding a medically efficacious compound, an energy source and an actuator driven by the energy source for temporarily and at intervals placing the compound in proximity to but not in contact with the skin of a subject such that during therapeutic use the sodium chloride shows:

(i) no metabolic change;

(ii) no chemical change; and

(iii) no diminution in its quantity in the device.

18. The device according to claim 17 adapted to be worn around the abdomen or thorax of a subject.

19. The device according to either of claims 17 or 18 wherein the energy source is a low voltage battery.

20. The device according to any of claims 17-19 further comprises an electronic timer.

21. The device according to any of claims 17-20 wherein the actuator is a spring return push-rod solenoid.

22. A device according to any of claims 17-21 adapted to hold sodium chloride.

23. A device according to any of claims 17-21 adapted to hold sodium chloride coated according to any of claims 7-11.

24. A preparation comprising a medically efficacious substance coated or otherwise enclosed by an agent that forms a liquid impermeable but gas permeable layer such that in use the medically efficacious substance shows:

(i) no metabolic change;

(ii) no chemical change; and

(iii) no diminution in its quantity in the preparation;

for use as a medicament..

25. A preparation according to claim 24, in a form selected from the group consisting of: a pill, a tablet, a lozenge, a bolus, a capsule, a caplet, a granule, a nanoparticle, and a microparticle.

26. A preparation according to claim 25, being in granular, nanoparticle or microparticle form selected from the group consisting of: a suspension, a cream, and a paste.

27. A preparation according to claim 24, prepared for use with a patch for holding said preparation near to or against the skin of a patient.

28. A preparation according to claim 24, prepared for implantation into the body of a patient.

29. A preparation according to any of claims 24-28, wherein said agent is selected from the group consisting of: a ceramic, a polymer, a natural wax, and beeswax hardened with cornstarch and talc.

30. A preparation according to any of claims 24-29, wherein said substance is selected from the group consisting of: sodium chloride, capsaicin, metformin, salicylic acid, and a derivative of salicylic acid.

31. A preparation according to any of claims 24-29, wherein said substance is selected from the group consisting of; a substance endogenous to the body, a food substance, a plant material, and a drug.

32. A preparation according to any of claims 24-31, combined with a preparation of at least one ingredient designed for delivery into solution.

33. A preparation according to any of claims 24-31 combined with a preparation of at least one ingredient designed for delivery into solution for a therapeutic purpose.

34. A method of manufacture of a medicament comprising coating or otherwise enclosing a medically efficacious substance in an agent that forms a liquid impermeable but gas permeable layer such that during therapeutic application in or on the body the medically efficacious substance shows:

(i) no metabolic change;

(ii) no chemical change; and

(iii) no diminution in its quantity in the formulation.